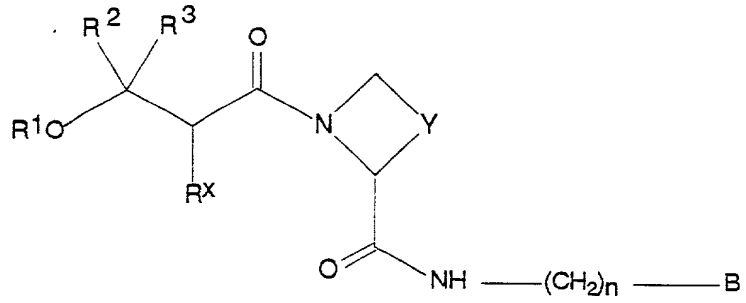
Claims

1. A compound of formula I,



I

wherein

R^1 represents H, $C(O)R^{11}$, $SiR^{12}R^{13}R^{14}$ or C_{1-6} alkyl which latter group is optionally substituted or terminated by one or more substituent selected from OR^{15} or $(CH_2)_qR^{16}$;

R^{12}, R^{13} and R^{14} independently represent H, phenyl or C_{1-6} alkyl;

R^{16} represents C_{1-4} alkyl, phenyl, OH, $C(O)OR^{17}$ or $C(O)N(H)R^{18}$;

R^{18} represents H, C_{1-4} alkyl or $CH_2C(O)OR^{19}$;

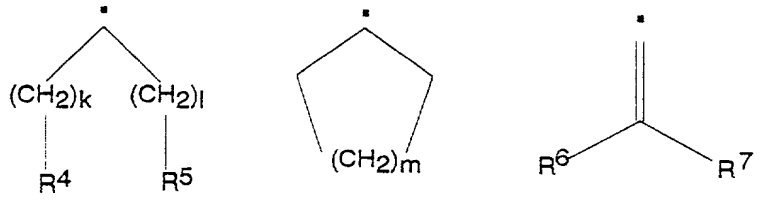
R^{15} and R^{17} independently represent H, C_{1-6} alkyl or C_{7-9} alkylphenyl;

R^{11} and R^{19} independently represent H or C_{1-4} alkyl; and

q represents 0, 1 or 2;

R^2 and R^3 independently represent H, C_{1-4} alkyl, cyclohexyl or phenyl;

R^x represents a structural fragment of formula IIa, IIb or IIc,



IIa IIb IIc

wherein

k, l and m independently represent 0, 1, 2, 3 or 4;

R^4 and R^5 independently represent H, $Si(Me)_3$, 1- or 2-naphthyl, a polycyclic hydrocarbyl group, $CHR^{41}R^{42}$ or C_{1-4} alkyl (which latter group is optionally substituted by one or more fluorine atoms), or C_{3-8} cycloalkyl phenyl, methylenedioxyphenyl, benzodioxanyl, benzofuranyl, dihydrobenzofuranyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, coumaranonyl, coumarinyl or dihydrocoumarinyl (which latter twelve groups are optionally substituted by one or more of C_{1-4} alkyl (which latter group is optionally substituted by one or more halo substituent), C_{1-4} alkoxy, halo, hydroxy, cyano, nitro, SO_2NH_2, C(O)OH or $N(H)R^{43}$);

R^{41} and R^{42} independently represent cyclohexyl or phenyl;

R^6 and R^7 independently represent H, C_{1-4} alkyl, C_{3-8} cycloalkyl, phenyl (which latter group is are optionally substituted by one or more of C_{1-4} alkyl (which latter group is optionally substituted by one or more halo substituent), C_{1-4} alkoxy, halo, hydroxy, cyano, nitro, SO_2NH_2, C(O)OH or $N(H)R^{44}$) or together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl ring;

R^{43} and R^{44} independently represent H or $C(O)R^{45}$; and

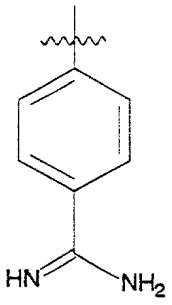
R^{45} represents H, C_{1-4} alkyl or C_{1-4} alkoxy;

Y represents CH_2, $(CH_2)_2$, CH=CH, $(CH_2)_3$, $CH_2CH=CH$ or $CH=CHCH_2$, which latter three groups are optionally substituted by C_{1-4} alkyl,

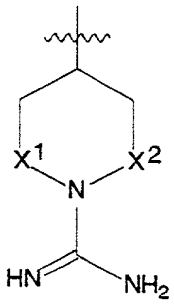
methylene, oxo or hydroxy;

n represents 0, 1, 2, 3 or 4; and

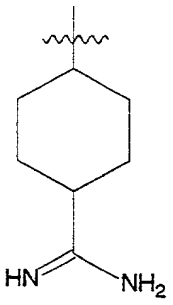
B represents a structural fragment of formula IVa, IVb or IVc



IVa



IVb



IVc

wherein

X^1 and X^2 independently represents a single bond or CH_2;

or a pharmaceutically acceptable salt thereof.

2. A compound of formula I, as defined in Claim 1, wherein when n represents 2 and B represents a structural fragment of formula IVb, X^1 and X^2 do not both represent CH_2.

3. A compound of formula I, as defined in Claim 1 or Claim 2, wherein R^1 represents optionally substituted C_{1-6} alkyl or H.

4. A compound of formula I, as defined in Claim 3, wherein R^1 represents H.

5. A compound of formula I, as defined in any one of the preceding

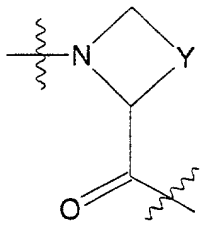
claims, wherein R^x represents a structural fragment of formula IIa.

6. A compound of formula I, as defined in any one of the preceding claims, wherein Y represents CH_2 or $(CH_2)_2$.

7. A compound of formula I, as defined in Claim 1 or any one of Claims 3 to 6, wherein n represents 1.

8. A compound of formula I, as defined in Claim 1 or any one of Claims 3 to 7, wherein B represents a structural fragment of formula IVa.

9. A compound of formula I, as defined in any one of the preceding claims, wherein the fragment



is in the S-configuration.

10. A compound as claimed in Claim 1 which is
(*R*)-PhCH(CH_2OH)-C(O)-Aze-Pab;
(*S*)-PhCH(CH_2OH)-C(O)-Aze-Pab;
(*R*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Aze-Pab;
(*S*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Aze-Pab;
(*R,S*)-3,4-dimethoxyphenyl-CH(CH_2OH)-C(O)-Aze-Pab;
(*R*)-2-naphthyl-CH(CH_2OH)-C(O)-Aze-Pab;
(*S*)-2-naphthyl-CH(CH_2OH)-C(O)-Aze-Pab;
(*R*)-PhCH(CH_2OH)-C(O)-Aze-Pig;
(*S*)-PhCH(CH_2OH)-C(O)-Aze-Pig;

(*R,S*)-PhCH(CH_2OH)-C(O)-Pro-(*R,S*)-Hig;

(*R*)-2,5-dimethoxyphenyl-CH(CH_2OH)-C(O)-Aze-Pab;

(*S*)-2,5-dimethoxyphenyl-CH(CH_2OH)-C(O)-Aze-Pab;

(*S*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R,S*)-3-aminophenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3-(methylamino)phenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-3-(methylamino)phenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-PhCH(CH_2OH)-C(O)-Pro-Pab;

(*R,S*)-3,5-dimethylphenyl-CH(CH_2OH)-C(O)-Aze-Pab;

(*S*)-3-(trifluoromethyl)phenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3-(trifluoromethyl)phenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R,S*)-3-hydroxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-((3-chloro-5-methylphenyl)-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-((3-chloro-5-methylphenyl)-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-3-fluorophenyl-CH(CH_2OH)CO-Pro-Pab;

(*R*)-3-fluorophenyl-CH(CH_2OH)CO-Pro-Pab;

(*S*)-3-chlorophenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3-chlorophenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R,S*)-3,5-dimethylphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-3,5-bis(trifluoromethyl)phenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3,5-bis(trifluoromethyl)phenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R,S*)-3-methoxy-5-methylphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R,S*)-(2,5-dimethoxyphenyl)-CH(CH_2OH)-C(O)-Pro-Pab;

(*R,S*)-(3,5-dimethoxyphenyl)-CH(CH_2OH)-C(O)-Pro-Pab;

(*R,S*)-3,4-(methylenedioxyphenyl)-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-3-(2-naphthyl)-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3-(2-naphthyl)-CH(CH_2OH)-C(O)-Pro-Pab;

(*R,S*)-3,5-dimethoxyphenyl-CH(CH_2OH)-C(O)-Aze-Pab;

(*R*,*S*)-2-chloro-5-aminophenyl-CH(CH_2OH)-C(O)-Aze-Pab;

(*R*)-3-methylphenyl-CH(CH_2OH)-C(O)-Aze-Pab;

(*S*)-3-methylphenyl-CH(CH_2OH)-C(O)-Aze-Pab;

(*R*)-2,5-dimethylphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-2,5-dimethylphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3-methoxy-4-hydroxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-3-methoxy-4-hydroxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3,5-dichlorophenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-3,5-dichlorophenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-2,3-dimethoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-2,3-dimethoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-3-methoxy-5-chlorophenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-3-methoxy-5-chlorophenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*)-2-methyl-5-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-2-methyl-5-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab;

(*R*,*S*)-Ph-C(Me)(CH_2OMe)-C(O)-Pro-Pab;

(*R*)-2-chloro-3-methylphenyl-CH(CH_2OH)-C(O)-Aze-Pab;

(*S*)-2-chloro-3-methylphenyl-CH(CH_2OH)-C(O)-Aze-Pab;

(*R*)-2,3-(methylenedioxyphenyl)-CH(CH_2OH)-C(O)-Pro-Pab;

(*S*)-2,3-(methylenedioxyphenyl)-CH(CH_2OH)-C(O)-Pro-Pab; or

(*R*,*S*)-Ph-C(Me)(CH_2OMe)-C(O)-Aze-Pab;

or a pharmaceutically acceptable salt thereof.

11. A compound of formula I, as defined in Claim 1, provided that when R^x represents a structural fragment of formula IIa, then R^4 and/or R^5 (as appropriate) do/does not represent phenyl substituted by halo-substitituted C_{1-6} alkyl.

12. A compound of formula I, as defined in Claim 1, provided that when R^x represents a structural fragment of formula IIa, then R^4 and/or R^5 (as

appropriate) do/does not represent methylenedioxyphenyl, benzodioxanyl, benzofuranyl, dihydrobenzofuranyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, coumaranonyl, coumarinyl or dihydrocoumarinyl.

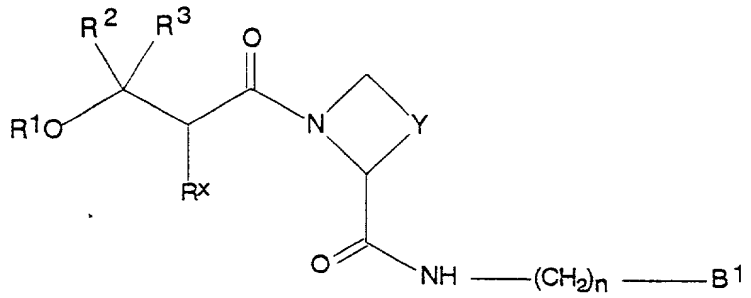
13. A compound of formula I, as defined in Claim 1, provided that when R^x represents a structural fragment of formula IIc, then R^6 and/or R^7 (as appropriate) represent(s) unsubstituted phenyl.

14. A compound of formula I, as defined in Claim 1, wherein, when R^x represents a structural fragment of formula IIa, then R^4 and/or R^5 (as appropriate) represent(s) phenyl substituted by halo-substituted C_{1-6} alkyl.

15. A compound of formula I, as defined in Claim 1, wherein, when R^x represents a structural fragment of formula IIa, then R^4 and/or R^5 (as appropriate) represent(s) methylenedioxyphenyl, benzodioxanyl, benzofuranyl, dihydrobenzofuranyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, coumaranonyl, coumarinyl or dihydrocoumarinyl.

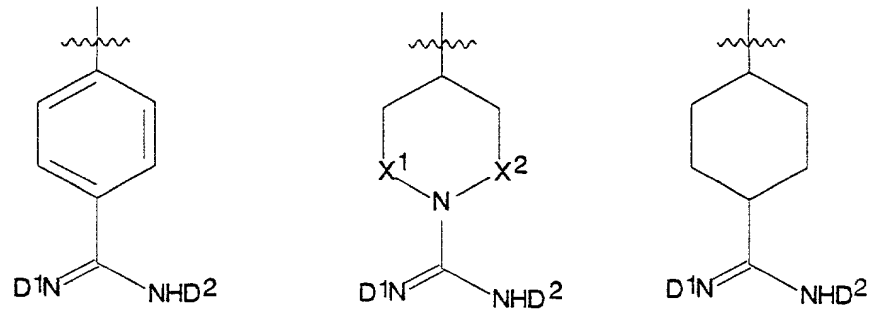
16. A compound of formula I, as defined in Claim 1, wherein, when R^x represents a structural fragment of formula IIc, then R^6 and/or R^7 (as appropriate) represent(s) substituted phenyl.

17. A compound of formula Ia,



Ia

wherein B^1 represents a structural fragment of formula IVd, IVe or IVf



IVd IVe IVf

wherein D^1 and D^2 independently represent H, OH, OR^a, $OC(O)R^b$, $OC(O)OR^c$, $C(O)OR^d$, $C(O)R^e$ and R^a, R^b, R^c, R^d and R^e independently represent phenyl, benzyl, $(CH_2)_2OC(O)CH_3$ or C_{1-6} alkyl which latter group is optionally interrupted by oxygen; and R^1, R^2, R^3, R^x, Y, n, X^1 and X^2 are as defined in Claim 1, or a pharmaceutically acceptable salt thereof, provided that D^1 and D^2 do not both represent H.

18. A compound of formula Ia, as defined in Claim 17, wherein D^1 represents H and D^2 represents OH, OCH_3, $OC(O)R^b$ or $C(O)OR^d$ and R^b and R^d are as defined in Claim 17.

19. A compound as claimed in Claim 17 which is

(*R*,*S*)-Ph-CH(CH_2OH)-C(O)-Pro-Pab-OH;

(*R*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Aze-Pab-OH;

(*S*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Aze-Pab-OH;

(*S*)-3-methoxyphenyl-CH(CH_2OH)CO-Pro-Pab(Z);

(*R*)-3-methoxyphenyl-CH(CH_2OH)CO-Pro-Pab(Z);

(*S*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab-OH;

(*R*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab-OH;

(*S*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab-OC(O)Et;

(*R*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab-OC(O)Et;

(*S*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab-$OC(O)CH_3$;

(*R*)-3-methoxyphenyl-CH(CH_2OH)-C(O)-Pro-Pab-OC(O)CH_3;
(*R*,*S*)-3-Ph-C(Me)(CH_2OMe)-C(O)-Pro-Pab(Z); or
(*R*,*S*)-3-methylphenyl-CH(CH_2OAc)-C(O)-Pro-Pab-OMe;
or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

21. A compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

22. A compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition where inhibition of thrombin is required.

23. A compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use in the treatment of thrombosis.

24. A compound of formula I as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use as an anticoagulant.

25. The use of a compound I as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof as active ingredient in the manufacture of a medicament for the treatment of a condition where inhibition of thrombin is required.

26. The use as claimed in Claim 25, wherein the condition is thrombosis.

27. The use of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, as active ingredient in the manufacture of an anticoagulant.

28. A method of treatment of a condition where inhibition of thrombin is required which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 19, or a pharmaceutically acceptable salt thereof, to a person suffering from, or susceptible to, such a condition.

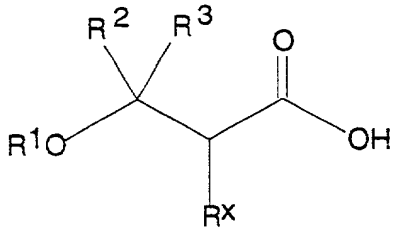
29. A method as claimed in Claim 28, wherein the condition is thrombosis.

30. A method as claimed in Claim 28, wherein the condition is hypercoagulability in blood and tissues.

31. The use of a compound as defined in any one if Claims 17, 18 or 19 as a prodrug.

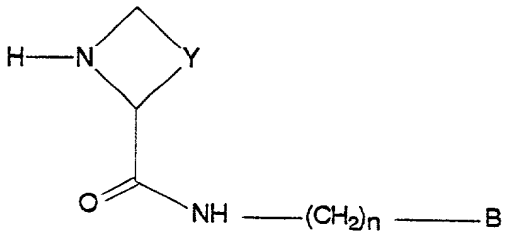
32. A process for the preparation of compounds of formula I which comprises:

(a) the coupling of a compound of formula V,



V

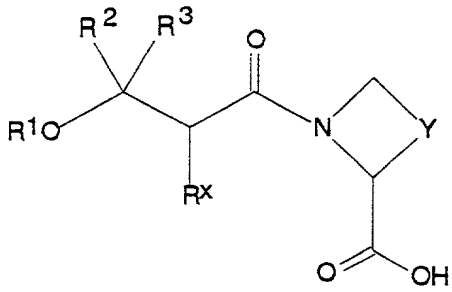
wherein R^1, R^2, R^3 and R^x are as defined in Claim 1, with a compound of formula VI,



VI

wherein Y, n and B are as defined in Claim 1; or

(b) the coupling of a compound of formula VII,



VII

wherein R^1, R^2, R^3, R^x and Y are as defined in Claim 1 with a compound of formula VIII,

$$H_2N\text{-}(CH_2)_n\text{-}B \qquad \text{VIII}$$

wherein n and B are as defined in Claim 1.